CORRELATION OF VASCULAR CHANGES WITH CHANGES IN MOTOR ACTIVITY AND SECRETION IN THE STOMACH OF MAN

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Received for publication July 22, 1942

The subject of our investigation was a man with a permanent gastric fistula 3.5 cm. in diameter, larger than that of Alexis St. Martin (1) or any other which has been studied in the past. His defect was the result of an operation done in 1895 and made necessary by a benign stricture of the esophagus. Despite the large communication to the outside world the appearance of the gastric mucosa both by direct inspection and gastroscopically was found to be normal (2). Secretory and motor functions of the stomach were average (2). Protruding through the defect and reflected on the abdominal wall around it is a collar of gastric mucosa. The width of this collar is made to vary with change in intra-abdominal pressure.

METHOD. Our subject came to the laboratory in the morning in a fasting state, and reclined for one-half hour on a cot before observations were begun. An effort was made to keep the subject's surroundings as neutral as possible and to keep him lightly diverted.

Circulatory changes. Changes in vascularity were readily recognized by variations in the color of the gastric mucous membrane. It was seen to undergo a very wide range of color changes under various circumstances, from a pale yellowish pink to a deep cardinal red. Changes of the same order and in the same direction occurred in the part of the mucosa within the cavity of the stomach and in that which lay exposed on the abdominal wall. Since it was simpler to obtain ideal lighting conditions on the outside, and since there a color scale could be brought up close to the mucosa for comparison, the recorded vascular changes are those observed in the collar of exposed mucous membrane under a cool, "soft white" fluorescent light suitably placed to provide constant lighting conditions. The standard colors used for comparison were quantitated by the method of Munsell. For convenience, however, the colors were given values from 10 to 100. The lower numbers corresponded to pale colors and the higher ones to deeper shades of red. It has been shown by a modification of the thermal gradient technic, described elsewhere (3) that these color changes do in reality reflect changes in blood flow.

It is important to note that accelerated blood flow in the mucosa was not merely associated with blushing of its surface. The membrane itself became wet, swollen, and turgid, and the rugae were slightly fuller and smoother. These evidences of vascular engorgement were especially obvious in the collar

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of mucosa exposed on the abdominal wall. During marked hyperemia, it often doubled in thickness from 5 mm. to 10 mm. and its radial folds decreased in number from 12 or 13 to 5 or 7. The tissue itself under such circumstances felt succulent and boggy.

Recording of gastric contractions. Records of contractions were obtained by the familiar technic of recording pressure changes in a balloon introduced into the stomach. It must be emphasized that this type of recording device measures only those contractions which alter the intragastric pressure. It has been suggested that certain peristaltic waves may course along the stomach without causing a change in intragastric pressure (4).

Collection of gastric juice. Continuous aspiration of the stomach contents was carried out through a small rubber tube accompanying the balloon. Collections made thus, when the walls of the stomach were held apart by the presence of the balloon, effected satisfactory emptying of the stomach. In the absence of the inflated balloon, however, the gastric juice collected in isolated folds of the collapsed stomach and was thus not thoroughly accessible to aspiration through a tube.

The completeness of the collection when the balloon was in place was confirmed by removing the balloon after collection of secretion through the tube, and rolling the patient over on his left side approximately 120°. No additional fluid poured out.

Analysis of gastric juice. The gross appearance of the specimens was noted. The degree, if any, of discoloration with bile was recorded. The relative concentration of mucus was estimated by noting the comparative viscosity of the fluid and the presence of shreds. Peptic activity was determined by the method of Mett (5). The concentration of acid was estimated by titration of the specimens against 0.1 N sodium hydroxide with Toepfer's solution and phenolphthalein as indicators of "free" and "total" acidity, respectively.

Estimation of parietal cell output. No method was available for the estimation of the output of hydrochloric acid by the parietal cells. Since acid is manufactured only by the parietal cells, however, it seemed clear that total hydrochloric acid was some function of volume of juice secreted within a specified time and the concentration of acid. Based on the relationship between hydrochloric acid and neutral chlorides in gastric juice established by Hollander (6), Gray (7) and others (8) (9), a formula was devised for the calculation of the approximate output of the parietal cells in terms of cubic centimeters of 0.166 N hydrochloric acid.

Reproduced in figure 1 is a modification of the curve established by Hollander for the relationship between hydrochloric acid and neutral chlorides in the gastric juice. Reference to the figure will show that the lower end of the line which relates the 2 constituents points near 166 millimoles of hydrochloric acid (total titratable acid of 166). A specimen of gastric juice containing this concentration of acid would consist of pure parietal secretion. At the other end of the curve, the constituents of the alkaline component are at a maximum, and there is no parietal secretion present. At a point half way along the ordi-

nate and abscissa, we are dealing with a solution containing a 50 per cent concentration of each of the constituents. Perpendiculars dropped from each of these points intersect at the midpoint of the curve. Therefore, at suitable intervals along the curve, perpendiculars may be dropped onto the abscissa to denote what per cent of solution of certain titratable "total acid" is actually made up of parietal cell secretion. Figures for total acid, of course, correspond numerically to millimoles of hydrochloric acid. Multiplying the percentage figure by the volume of gastric juice secreted within a given time yields the approximate quantity of parietal cell secretion elaborated during that period.

Sources of error in calculation for parietal cell output. The value thus obtained would, of course, not be entirely accurate since the curve illustrated was estab-

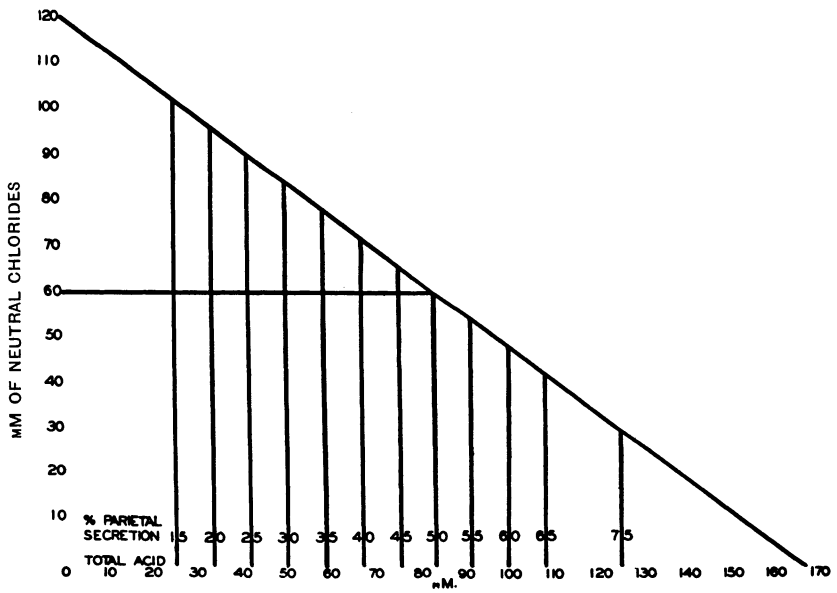

Fig. 1. Curve illustrating the relation between neutral chlorides and hydrochloric acid in the gastric secretion. (Modified from Hollander.)

lished on the basis of a statistical relationship, and individual specimens must be expected to vary slightly from the mean. Furthermore, the calculations were based on analyses of pure gastric juice in a blind stomach pouch. Any admixture of the juice with saliva or bile or any loss of juice through the pylorus would introduce a source of error. In this particular case, of course, the gastric juice could not be contaminated by saliva since the esophagus was completely occluded. Contamination of the juice with duodenal contents was easily recognized by the bile tint and such specimens were not included in calculations of parietal cell activity. Loss of secretion by emptying through the pylorus, however, was a persistent source of error. It always influenced the calculations in the same direction, however, and since emptying occurred only during periods of active motility (2), in the absence of vigorous gastric contractions the error became negligible.

CORRELATION OF FUNCTIONS. 1. *Basal state.* Carlson (10) has shown that during the resting "basal" state the stomach undergoes periodic phases of intense contractile activity alternating with phases of relative quiescence. This same periodicity of function we have noted in the activity of the acid secreting cells and in the vasomotor activity in the stomach.

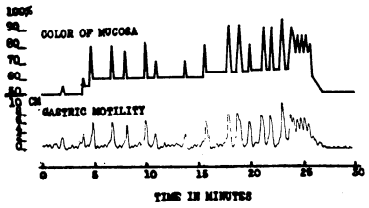

Fig. 2. Typical pattern of a phase of accelerated gastric motility with characteristic ending in a period of incomplete tetanus. Note changes in color of the mucosa associated with vigorous contractions.

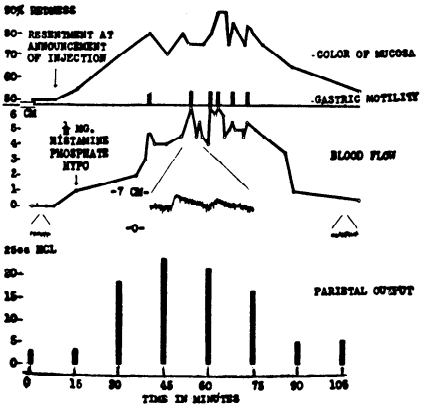

Fig. 3. Correlation of gastric functions including recorded blood flow following histamine injections.

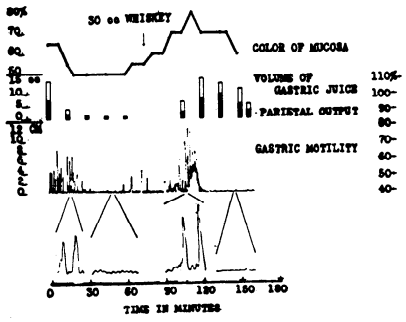

Fig. 4. Effect of alcohol on gastric function. Whiskey was administered following a period of spontaneous accelerated gastric function. Normally, a second such period would not follow for at least 2 hours.

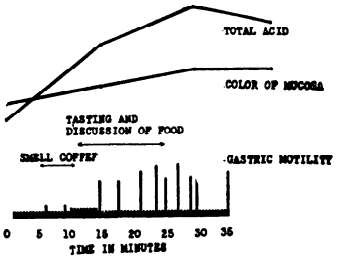

Fig. 5. Gastric function associated with stimulation of appetite.

Figs. 2–5

In the above figures the designation "Parietal output" indicates the volume of HCl at concentration 0.166 N.

The "basal" waves of low amplitude were not found to be accompanied by any detectable change in the color of the mucous membrane of the stomach. The more vigorous contractions, however, were associated with a simultaneous transitory blushing of the mucosa proportional in degree to the force of the contraction. Figure 2 shows the correlation of color changes in the mucosa with vigorous contractions of the stomach wall.

Like blood flow the rate of acid production in the stomach was accelerated

during phases of vigorous contractions and relatively slow during quiescent phases.

Comment. The occurrence of these spontaneous periodic phases of accelerated gastric function was carefully taken into account when vascular changes and changes in secretion and motility were attributed to the influence of stimuli applied experimentally. Usually such stimuli were applied shortly after the termination of one of these phases, when another would not be expected for an hour and a half. In addition, the experiments were repeated sufficiently often to establish the validity of the inferences.

Agents well known to cause an acceleration of acid secretion were tested for their effects on motor activity and vascularity in the stomach.

Effect of histamine on blood flow, acid secretion and motor activity. During a half-hour control period the gastric juice was collected and the color of the mucosa was observed. In addition a thermal gradientometer described elsewhere (3) was in place inside the stomach to measure changes in blood flow. Thus it was possible to correlate blood flow with color changes.

After the establishment of a base line, 0.0005 gram of histamine phosphate was injected hypodermically.

The results are charted in figure 3. Within 5 to 10 minutes of the injection the red color of the mucosa became deeper and there was a parallel increase in recorded blood flow. At the same time acid output increased in terms of parietal cell secretion and total titratable acid. It can readily be seen in the figure that the parietal cell output parallels the vascular changes.

Within 25 minutes after histamine injection strong contractions of the stomach wall occurred. With each of these there was a transitory blushing of the mucosa and an increase in recorded blood flow.

The maximum effect from histamine in terms of secretion, blood flow and motility occurred in about 45 minutes. After 90 minutes the effects had nearly subsided and the values had returned to normal by 2 hours.

Comment. These data illustrate: 1. That vascular changes observed as variations in color of the exposed gastric mucous membrane actually reflect changes in blood flow. 2. That histamine stimulated an increase in blood flow and motility as well as in acid production. 3. The importance of expressing acid output in terms of parietal cell secretion, since the "total acid" concentration failed to fall to control levels following a phase of accelerated secretion when acid output had subsided.

Effects of alcohol. After establishing a base line of vascularity, secretion and motor activity, 30 cc. of 90 proof whiskey (45 per cent alcohol by volume) was introduced into the stoma. As in the case of histamine an acceleration of all three functions occurred. The maximum effect was observed in 45 minutes, and in 90 minutes the values had returned to normal. A typical experiment is illustrated graphically in figure 4.

Comment. Other workers (10, 11) have shown that alcohol need not be introduced directly into the stomach in order to stimulate the parietal cells to accelerated activity. Given intravenously or rectally the drug causes a

sharply increased output of acid. Our observations indicate that even when ingested, the effects are not the result of local stimulation. Hyperemia of the mucosa and accelerated secretion did not occur until the drug had had time to become absorbed.

Effects of beef juice. Similar observations were recorded when a beef bouillon cube was introduced into the stoma. Within 15 minutes there occurred a flushing of the mucosa with enhanced secretory and motor activity which lasted more than an hour.

Preparation for eating. Another circumstance known to be associated with accelerated acid output is the feeling of good appetite which accompanies the sight or mere thought of delectable food. This was found to be also associated with hyperemia and hypermotility as illustrated in figure 5. The vascular engorgement, accelerated acid production and increased motor activity occurred promptly following the mention of appetizing food. Actual presentation and tasting of the food added little to this effect.

Hunger. Although, occasionally, hunger pains were reported by the subject at times in the absence of stomach contractions (2), as a rule they were found to be accompanied by vigorous contractions and a relatively red, actively secreting mucosa.

CORRELATION OF BLOOD FLOW, ACID PRODUCTION AND MOTOR ACTIVITY. *General statement.* While profound changes in blood flow, acid production and motor activity have been observed accompanying various emotional states and other circumstances, never in this subject were changes in vascularity and acid secretion dissociated. An increase in one was found under all circumstances to be associated with an increase in the other. Conversely, low acid output and pallor of the mucosa have been regularly associated. Vigorous motility has never been observed when the color of the mucosa was 50 or below. In the presence of red mucosa, vigorous contractions might or might not occur. No correlation was observed between the degree of hyperemia and the height or frequency of contractions, but accompanying each one was noted a transitory increase in redness of the mucosa, which subsided with the relaxation of the stomach wall.

DISCUSSION. Doubtless, enhanced secretory and motor activity in the stomach requires added work by the cells of the stomach wall. Davenport and Fisher (13) have shown that in secreting acid, work is done by the cells of the gastric mucosa to the extent of 800 calories per liter of secretion. Others (14, 15, 16, 17) have found in animals and humans low values for gastric acidity during states of anoxemia induced by high altitude, low oxygen tension chambers severe hemorrhage, and even polycythemia. Correction of the anoxic state resulted in a return of acidity values to normal.

All of this suggests that hyperfunction of the stomach would be accompanied by hyperemia, and indeed it is a general biological experience that heightened cellular metabolism requires increased blood flow.

A few investigators (18, 19) have recorded combined measurements of blood flow and gastric secretion in animals. Lim, Necheles and Ni (18) studied gastric blood flow in the excised dog's stomach, perfusing it with another dog's

blood. They demonstrated acid secretion following histamine injections. The blood flow, as measured by cannulating the veins, failed to parallel the rate of secretion.

Dodds and his co-workers (19) made similar studies on dogs after surgical intervention. Instead of resecting the stomach, they left it in place and resected the entire small and large intestine. Following this, appropriate vessels to the stomach were cannulated, and the blood flow was measured by collecting the venous blood in a graduated container for a certain length of time. The blood was then transfused back into the animal. Their findings differed widely from those of Lim et al. An increase in blood flow was noted with an increase of volume of gastric juice secreted in response to histamine injection. They were able to inhibit the histamine effect with regard to volume of gastric secretion and blood flow by giving injections of pitressin or barium chloride, or by causing a vasoconstriction in the stomach by irrigating it with cold water. The titratable acidity, however, remained high.

In the interpretation of all of these animal experiments, one must reckon with the trauma of surgical operation, the effects of anesthesia, and the pathological changes secondary to the operative procedure.

A few observations have been made on circulatory changes in the gastrointestinal tract by direct inspection of the serosal and mucosal coats. Kuntz and Hazelwood (20) found that a reflex vasoconstriction in the serosal coat of the intestine of the cat was induced by packing ice on the abdominal wall. Warming the abdomen was found to cause a vasodilatation in the serosa.

Beaumont (1) recognized in Alexis St. Martin that the stomach lining was redder at some times than at others. "On the application of aliment," he wrote, "the action of the vessels is increased, the color brightened. . . ." Anger and fear, he noted, produced a "morbid" appearance of the mucosa, although it is not entirely clear from his notes whether under those conditions the stomach was redder or paler. Carlson (10) observed in his Mr. V. a deepening of the red color of the mucosa with each strong contraction of the stomach wall. Schindler (21) has described the appearance of the stomach mucosa of patients with peptic ulcers as appearing redder than "normal" through the gastroscope. This instrument has not been left in place long enough to follow changes in color for more than a few minutes at a time.

Drury, Florey and Florey (22) studied vasomotor changes in a patch of exteriorized colon in dogs. They found with alarm or fright a uniform blanching of the mucosa, due presumably to constriction in the large branches of the mesenteric arteries. Barcroft and Florey (23) using similar preparations found pallor marked during brief spurts of running, but less marked during prolonged exercise. They also found pallor in association with "anxiety" or "excitement."

Our studies support these findings—that profound vascular changes occur in the gastric mucosa and, in addition, that hyperemia occurs in association with accelerated acid secretion and motor activity, and pallor with a decrease in these functions.

SUMMARY. Simultaneous observations of motor activity, vascularity, and

secretion in the stomach have been recorded. During the resting state, the stomach was found to be relatively pale and contracting with rhythmic waves of low amplitude. Acid was secreted continuously in small amounts. From time to time there occurred spontaneous phases of hyperemia, hypermotility and hypersecretion.

The effects of histamine and other stimuli on the various gastric functions were recorded. A direct association between vascularity (blood flow) and acid production was found to obtain under all circumstances of accelerated or depressed activity. Vigorous contractions, while they did not invariably accompany redness of the mucosa, never occurred in the presence of pallor.

CONCLUSIONS

1. Studies have been pursued on a subject with a large gastric fistula whose peculiar defect provided the opportunity to collect at intervals the total volume of secretion in the stomach.

2. The rate of acid production in the stomach was estimated under varying conditions with reference to volume of secretion and concentration of acid. The results were expressed in terms of parietal cell output.

3. Increased parietal cell output was always associated with hyperemia of the gastric mucosa. Hyperaemia also accompanied increased motor activity.

4. On the basis of data gathered from these studies, certain generalizations are possible with regard to the interpretation of the findings on routine gastric analyses performed on patients.

a. When an unusually large volume of gastric juice of high titratable acidity accumulates in an unobstructed stomach during a specified interval, it is safe to assume that the mucous membrane is relatively red and that no vigorous contractions are taking place in the stomach.

b. When a small volume of gastric juice of very high titratable acidity is obtained under similar circumstances, it is likely that the mucous membrane is relatively engorged with blood and that, in addition, especially vigorous contractions are taking place.

c. Low acid values in the presence of small volumes of gastric juice strongly suggest that the gastric mucosa is relatively pale and that no vigorous contractions are taking place.

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